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Chapter 56: Obesity

INTRODUCTION

- *Obesity* occurs when there is an imbalance between energy intake and energy expenditure over time, resulting in increased energy storage.
- The etiology of obesity is multifactorial, with genetic and environmental factors contributing to various degrees.
- Medical conditions associated with weight gain include iatrogenic and idiopathic Cushing syndrome, growth hormone deficiency, insulinoma, leptin and melanocortin 4 (MC4) receptor deficiency, and psychiatric disorders such as depression, binge-eating disorder, and schizophrenia. Genetic syndromes that are associated with obesity, such as Prader–Willi syndrome, are extremely rare.
- Examples of medications associated with unintended weight gain include insulin, corticosteroids, some antidepressants, atypical and conventional antipsychotics, and several antiseizure medications.
- An understanding of the relationships among the brain, its many neurotransmitters and neuropeptides, environmental stimulation of brain activities, and other hormones relative to appetite is still evolving.
- The degree of obesity is determined by the net balance of energy ingested relative to energy expended over time. The single largest determinant of energy expenditure is metabolic rate, which is expressed as *resting energy expenditure* or *basal metabolic rate*. The most variable component of total energy expenditure is physical activity.

CLINICAL PRESENTATION

- Obesity is associated with serious health risks and increased risk of all-cause mortality. Central obesity reflects high levels of intra-abdominal or visceral fat associated with the development of hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease (sometimes referred to as "metabolic syndrome").
- Body mass index (BMI; calculated as weight [kg] divided by the square of the height [m^2]) and waist circumference (WC; narrowest circumference between the last rib and the top of the iliac crest) are the best clinical indicators of excess body fat that independently predict disease risk (**Fig. 56-1**).

FIGURE 56-1

Assessment of obesity according to the Edmonton Obesity Staging System (EOSS) and classification of overweight and obesity by body mass index, comorbidity risk, waist circumference, and associated disease risk.

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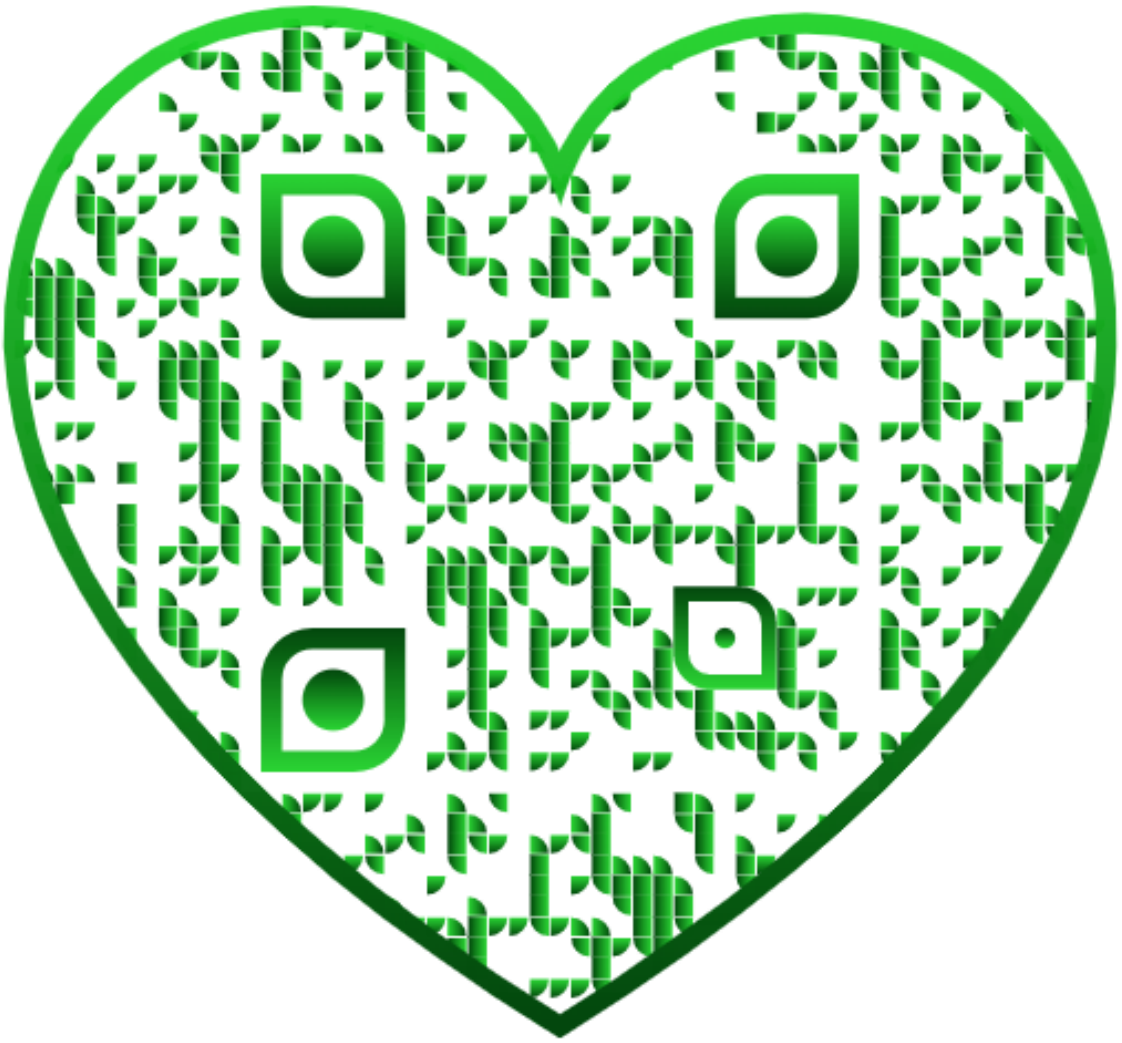

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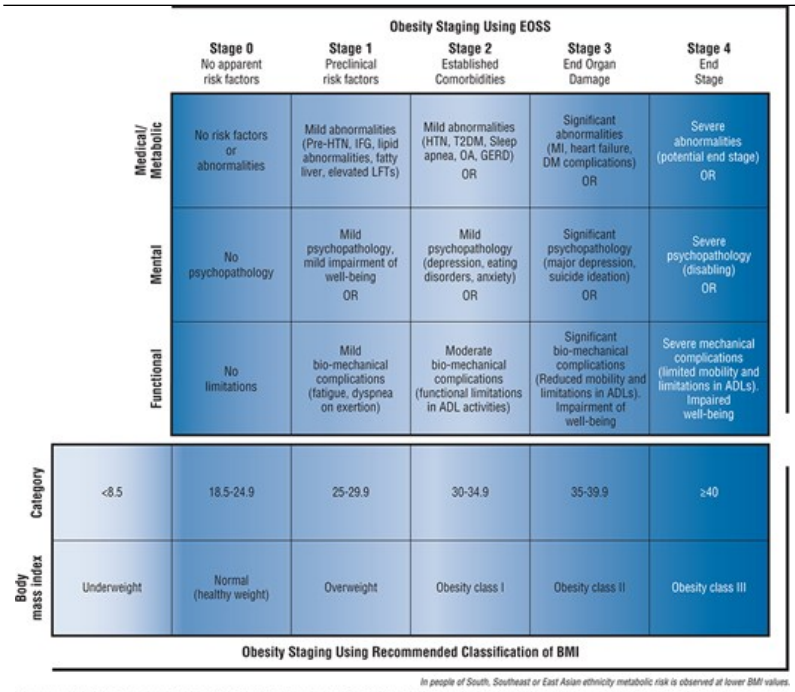
Obesity Staging Using EOSS
Stage 0
No apparent risk factors
Stage 1
Preclinical risk factors
Stage 2
Established Comorbidities
Stage 3
End Organ Damage
Stage 4
End Stage
Medical/ Metabolic
No risk factors or abnormalities
Mild abnormalities (Pre-HTN, IFG, lipid abnormalities, fatty liver, elevated LFTs)
Mild abnormalities (HTN, T2DM, Sleep apnea, OA, GERD) OR
Significant abnormalities (MI, heart failure, DM complications) OR
Severe abnormalities (potential end stage) OR
Mental
No psychopathology
Mild psychopathology, mild impairment of well-being OR
Mild psychopathology (depression, eating disorders, anxiety) OR
Significant psychopathology (major depression, suicide ideation) OR
Severe psychopathology (disabling) OR
Functional
No limitations
Mild bio-mechanical complications (fatigue, dyspnea on exertion)
Moderate bio-mechanical complications (functional limitations in ADL activities)
Significant bio-mechanical complications (Reduced mobility and limitations in ADLs). Impairment of well-being
Severe mechanical complications (limited mobility and limitations in ADLs). Impaired well-being
Body mass index
Category
<8.5
18.5-24.9
25-29.9
30-34.9
35-39.9
≥40
Underweight
Normal (healthy weight)
Overweight
Obesity class I
Obesity class II
Obesity class III
Obesity Staging Using Recommended Classification of BMI
In people of South, Southeast or East Asian ethnicity metabolic risk is observed at lower BMI values.
Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Lisa M. Holle, Cecily V. DiPiro: *DiPiro's Pharmacotherapy Handbook, 13th Edition*
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TREATMENT

- Goals of Treatment: Current clinical practice guidelines recommend a "complication-centric approach" to assess weight-related complications to determine appropriate treatment and intensity in individuals with overweight and obesity. The primary goal is to ameliorate weight-related complications and ultimately improve health and quality of life rather than a preset decrease in body weight.

GENERAL APPROACH

- Successful obesity treatment includes comprehensive lifestyle changes—healthy diet, adequate physical activity, and behavior modification—as the cornerstone of obesity management. Set weight goals consistent with medical needs, weight-related complications, and patient's personal preferences.
- Current adult guidelines recommend reduced energy intake through adherence to a low-calorie diet (LCD). Adherence to the LCD with increased exercise and in-person behavioral counseling sessions result in an average weight loss of 8% over 6 months.
- Bariatric surgery, which reduces the stomach volume or absorptive surface of the alimentary tract, remains the most effective intervention for obesity.
- Implantable medical devices are an option for individuals who do not qualify for bariatric surgery or choose to not undergo the procedure. They work in conjunction with prescribed diet and exercise programs.

PHARMACOLOGIC THERAPY

- Pharmacotherapy is an adjunct to comprehensive lifestyle intervention in adults who are motivated to lose weight, have failed to achieve or sustain weight loss with lifestyle change alone, and have a BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related comorbidity (**Table 56-1**).
- Long-term pharmacotherapy may have a role for patients who have no contraindications to approved drug therapy (**Table 56-2**). Guidelines recommend discontinuation of medication therapy after 3 months if insufficient body weight is lost or significant adverse reactions are experienced.

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- **Orlistat** (180 or 360 mg in three divided doses/day) is a lipase inhibitor that induces weight loss by lowering dietary fat absorption; it also improves lipid profiles, glucose control, and other metabolic markers. Soft stools, abdominal pain or colic, flatulence, fecal urgency, and/or incontinence occur in up to 80% of individuals using prescription strength, are mild to moderate in severity, and improve after 1–2 months of therapy. Orlistat is approved for long-term use. It interferes with the absorption of fat-soluble vitamins, **cyclosporine, levothyroxine**, and **antiretrovirals**. A nonprescription formulation is also available.

- **Phentermine** in combination with **topiramate extended-release** is indicated for chronic weight management. Doses are gradually titrated from phentermine 3.75 to 15 mg and topiramate 23 to 92 mg over 4 months, but the drug should be stopped after 12 weeks if 5% weight loss is not achieved with the 7.5-mg phentermine and 46-mg topiramate dose. Common adverse effects include constipation, dry mouth, paresthesia, dysgeusia, and insomnia.

- **Naltrexone** in combination with **bupropion extended-release** is indicated for chronic weight management. Increase dose gradually over 4 weeks, starting with one tablet daily (8 mg naltrexone/90 mg bupropion) to a maintenance dose of two tablets twice daily. Patients should avoid taking their dose with a high-fat meal. Common adverse effects include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea. Discontinue treatment if 5% weight loss is not achieved after 12 weeks.

- **Liraglutide** and **semaglutide** are glucagon-like peptide-1 (GLP-1) receptor agonists indicated for chronic weight management. See **Table 56-1** for dose escalation schedules to improve tolerability of gastrointestinal adverse effects. Both are administered subcutaneously and available in prefilled, multidose pens. Common adverse effects include nausea, diarrhea, constipation, vomiting, dyspepsia, hypoglycemia, and abdominal pain. Discontinue liraglutide if weight loss of at least 4% is not achieved after 16 weeks.

- **Tirzepatide** is a dual GLP-1 agonist and glucose-dependent insulinotropic polypeptide-1 agonist for chronic weight management. Start with 2.5 mg weekly subcutaneously for 4 weeks; titrate dose every 4 weeks to a maximum of 15 mg weekly. Adverse medication reactions are similar to other GLP-1 agents and include nausea, diarrhea, constipation, vomiting, dyspepsia, and abdominal pain.

TABLE 56-1

FDA-Approved Pharmacotherapeutic Agents for Weight Loss

Medication	Brand Name	Initial Dose	Usual Dose	Special Population Dose	Comments
GI Lipase Inhibitor					
Orlistat	Xenical	120 mg three times daily with each main meal containing fat	120 mg three times daily with each main meal containing fat	Approved for adolescents ages 12 years or older	• Approved for long-term use • Take during or up to 1 hour after the meal • Omit dose if meal is occasionally missed or contains no fat
Orlistat	Alli[a]	60 mg three times daily with each main meal containing fat	60 mg three times daily with each main meal containing fat		
Phentermine–Topiramate Combination					

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Phentermine and topiramate extended-release	Qsymia	3.75 mg of phentermine and 23 mg of topiramate once daily for 14 days; then increase to 7.5 mg of phentermine and 46 mg of topiramate once daily	7.5 mg of phentermine and 46 mg of topiramate once daily to a maximum dose of phentermine 15 mg and topiramate 92 mg once daily	Maximum dose for patients with moderate or severe kidney impairment or patients with moderate hepatic impairment is 7.5 mg of phentermine and 46 mg of topiramate Approved for adolescents ages 12 years or older	• Approved for long-term use • Take dose in the morning to avoid insomnia • Controlled substance: C–IV
Naltrexone–Bupropion Combination					
Bupropion and naltrexone extended-release	Contrave	8 mg naltrexone/90 mg bupropion (one tablet) once daily in the morning for 1 week; then 8 mg naltrexone/90 mg bupropion twice daily (morning and evening) for 1 week; then 16 mg naltrexone/180 mg bupropion in the morning and 8 mg naltrexone/90 mg bupropion in the evening for 1 week; then 16 mg naltrexone/180 mg bupropion twice daily (morning and evening)	16 mg naltrexone and 180 mg bupropion (two tablets) twice daily	• Maximum dose for patients with moderate or severe kidney impairment is 8 mg naltrexone/90 mg bupropion (one tablet) twice daily • Maximum dose for patients with hepatic impairment is 8 mg naltrexone/90 mg bupropion (one tablet) once daily in the morning	• Approved for long-term use • Do not take dose with high-fat meal
Glucagon-Like Peptide-1 Agonists					

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Liraglutide	Saxenda	• 0.6 mg once daily for 1 week • 1.2 mg once daily for 1 week • 1.8 mg once daily for 1 week • 2.4 mg once daily for 1 week • 3.0 mg once daily for 1 week • Administered by subcutaneous injection	3 mg once daily	Use with caution in mild, moderate, and severe kidney and hepatic impairment. Approved for adolescents ages 12 years or older Pediatric patients who cannot tolerate 3 mg daily can receive a reduced dose of 2.4 mg daily	• Approved for long-term use • Inject subcutaneously in the abdomen, thigh, or upper arm • Administer at any time of day without regard to the timing of meals
Semaglutide	Wegovy	• 0.25 mg once weekly for 4 weeks • 0.5 mg once weekly for 4 weeks • 1 mg once weekly for 4 weeks • 1.7 mg once weekly for 4 weeks • 2.4 mg once weekly • Administered by subcutaneous injection	1.7–2.4 mg once weekly	Approved for adolescents ages 12 years or older	• Approved for long-term use • Approved for reduction in the risk of major adverse cardiovascular events in adults with obesity or overweight • Inject subcutaneously in the abdomen, thigh, or upper arm • Administer on the same day each week at any time of day without regard to the timing of meals
Glucagon-Like Peptide-1 and Glucose-Dependent Insulinotropic Polypeptide (GIP) Agonist					

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Tirzepatide	Zepbound	• 2.5 mg once weekly for 4 weeks • 5 mg once weekly for 4 weeks • Increase dose in 2.5 mg increments once weekly after at least 4 weeks on current dose up to 15 mg/wk • Administered by subcutaneous injection in abdomen, thigh, or upper arm	5 mg, 10 mg, or 15 mg once weekly. Maximum dose is 15 mg once weekly	Approved for adolescents ages 12 years or older	• Administer once weekly on the same day each week at any time of day without regard to meals • Rotate injection sites with each dose
MC4 Receptor Agonist					
Setmelanotide	Imcivree	• Adults and adolescents >12 years with specific genetic defects (see comments): • 2 mg once daily for 2 weeks, then increase to 3 mg once daily if tolerated and additional weight loss is desired (or decrease to 1 mg once daily based on tolerability) • Children aged 6 to <12 years: • 1 mg once daily for 2 weeks, then increase to 2 mg once daily if tolerated (or decrease to 0.5 mg once daily based on tolerability), then increase to 3 mg once daily if tolerated and additional weight loss is desired • Administered by subcutaneous injection	2–3 mg once daily	Not recommended for patients with moderate-to-severe kidney impairment	• Approved for long-term use in patients aged 6 years and above only for people with genetically confirmed deficiency of, PCSK1, or LEPR, or who have the Bardet–Biedl syndrome by clinical criteria • Inject subcutaneously in the abdomen, thigh, or upper arm rotating sites each day • Administer at the beginning of the day without regard to timing of meals
Noradrenergic Agents					
Phendimetrazine	Bontril PDM, Bontril Slow-Release	• Conventional tablet: start at 17.5 mg two or three times daily, given 1 hour before meals • Extended-release capsule: 105 mg once daily 30–60 minutes before morning meal	70–105 mg/day	Use caution in patients with kidney impairment	• Approved for short-term monotherapy • Controlled substance: C–III • Prescriptions should be written for the smallest quantity to

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					minimize possibility of overdose
Phentermine	Lomaira, Adipex-P	• 8 mg three times daily, given ½ hour before meal • Orally disintegrating tablet: 15 or 30 mg once every morning • Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	• 8 mg three times daily, given ½ hour before meal • Orally disintegrating tablet: 15 or 30 mg once every morning • Phentermine hydrochloride: 15–37.5 mg/day given in one or two divided doses; administer before breakfast or 1–2 hours after breakfast	Use with caution in patients with kidney impairment	• Approved for short-term monotherapy • Controlled substance: C–IV • Prescriptions should be written for the smallest quantity to minimize possibility of overdose • Individualize to achieve adequate response with lowest effective dose
Diethylpropion	Tenuate, Tenuate Dospan	• Immediate release: 25 mg three times daily administered 1 hour before meals • Controlled release: 75 mg once daily administered at midmorning	75 mg/day	Use with caution in patients with kidney impairment	• Approved for short-term monotherapy • Dose should not be administered in the evening or at bedtime • Controlled substance: C–IV

GI, gastrointestinal; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

[a]Available without a prescription.

TABLE 56-2

Clinical and Economic Considerations for Long-term Pharmacotherapy Options

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Medication	Percentage of Initial Body Weight Lost After 12 Months of Treatment[a]	Comments
Orlistat	7%	• Use may be limited by GI intolerance
Phentermine and topiramate extended-release	10%	• Limited distribution under FDA Risk Evaluation Mitigation Strategy (REMS) • Reports of new or worsening depression, suicidal thoughts or behaviors, and changes in mood
Bupropion and naltrexone extended-release	7%	• Lowers seizure threshold (bupropion) • Rare reports of hepatotoxicity (naltrexone) • Drug interactions with opioids, CYP2B6 inducers, and CYP2D6 substrates • Associated with serious neuropsychiatric reactions and an increased risk of suicidal thoughts and behavior when used for smoking cessation and treatment of depression
Liraglutide	7%	• Injectable (daily dosing) • Available as prefilled dosing pen • Reduces HbA1c and fasting glucose • Risk of medullary thyroid carcinoma (MTC) and multiple endocrine neoplasia syndrome type 2 (MEN2) • Rare reports of pancreatitis, gallbladder disease, and suicidal ideation
Semaglutide	16%	• Injectable (weekly dosing) • Available as prefilled dosing pen • Reduces HbA1c and fasting glucose • Risk of MTC and MEN2 • Rare reports of pancreatitis, gallbladder disease, and suicidal ideation
Tirzepatide	20%	• Injectable (weekly dosing) • Available as prefilled dosing pens • Reduces HbA1c and fasting glucose • Risk of MTC and MEN2 • Rare reports of pancreatitis, gallbladder disease, and suicidal ideation
Setmelanotide	23.1% (patients with POMC or PCSK1 deficiency) 9.7% (patients with LEPR deficiency)	• Injectable (daily dosing) • Available as multiple-dose vial (10 mg/mL) • Indicated for genetically confirmed or suspected deficiency POMC, PCSK1, or LEPR, or a clinical diagnosis of Bardet–Biedl syndrome

FDA, Food and Drug Administration; HbA1c, hemoglobin A1c.

[a]Efficacy data from subjects without type 2 diabetes.

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- **Setmelanotide** is a peptide analog of endogenous alpha-melanocyte stimulating hormone approved for chronic weight management in patients with genetically confirmed or suspected proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) abnormalities. Administer once daily subcutaneously starting with 2 mg daily for those 12 years and older and 1 mg daily for children aged 6 to less than 12 years; increase to 3 mg daily if tolerated. Common adverse effects include injection site reactions, skin hyperpigmentation, nausea, headache, diarrhea, abdominal pain, and spontaneous penile erections. Discontinue setmelanotide if weight loss of 5% is not achieved after 12–16 weeks.
- Many complementary and alternative therapy products are promoted for weight loss. Regulation of dietary supplements is less rigorous than that of prescription and over-the-counter drug products; manufacturers do not have to prove safety and effectiveness prior to marketing.

EVALUATION OF THERAPEUTIC OUTCOMES

- Assess progress monthly for the first 3 months, then every 3 months. Each encounter should document weight, WC, BMI, blood pressure, medical history, and patient assessment of drug tolerance.
- Diabetic patients require more intense medical monitoring and self-monitoring of blood glucose. Weekly healthcare visits for 1–2 months may be necessary until the effects of diet, exercise, and weight loss medication become more predictable.
- Monitor patients with hyperlipidemia or hypertension to assess effects of weight loss on appropriate end points.

See Chapter 103, Obesity, authored by Amy H. Sheehan, Judy T. Chen, Seena L. Haines, and Jack A. Yanovski, for a more detailed discussion of this topic.

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